

Title: Therapeutic and Diagnostic Tools for Impaired Glucose

**Tolerance Conditions** 

Applicant(s): Gary Ruvkun et al. Filing Date: April 27, 2001 Serial No.: 09/844,353 Page 1 of 16 Customer No.: 21559

1 ggtttaatta cccaagtttg agctccaaga gcacacatct gatcgtcgga 51 ttctactgta ctccccgaaa aaccaacaaa aaacacaagt ttttgaacac 101 ttgtaaatgc agacagaacg atgacgagaa tgaatattgt cagatgtcgg 151 agacgacaca aaattttgga aaatttggaa gaagagaatc tcggcccgag 201 ctgctcgtcg acgacttcaa caaccgctgc caccgaagct ctcggaacaa 251 ccactgagga tatgaggctt aagcagcagc gaagctcgtc gcgtgccacg 301 gagcacgata ttgtcgacgg caatcaccac gacgacgagc acatcacaat 351 gagacggctt cgacttgtca aaaattcgcg gacgcggcgt agaacgacgc 401 ccgattcaag tatggactgc tatgaggaaa acccgccatc acaaaaactt 451 caataaatta ttcttggatt tctaaaaagt catcaatgac gtcattaatg 501 cttttactgc tattcgcttt tgtacagccg tgtgcctcaa tagtcgaaaa 551 acgatgcggc ccaatcgata ttcgaaatag gccgtgggat attaagccgc 601 aatggtcgaa acttggtgat ccgaacgaaa aagatttggc tggtcagaga 651 atggtcaact gcacagtggt ggaaggttcg ctgacaatct catttgtact 701 gaaacacaag acaaaagcac aagaagaaat gcatcgaagt ctacagccaa 751 gatattccca agacgaattt atcacttttc cgcatctacg tgaaattact 801 ggaactctgc tcgtttttga gactgaagga ttagtggatt tgcgtaaaat 851 titcccaaat cttcgtgtaa ttggaggccg ttcgctgatt caacactatg 901 cgctgataat ttatcgaaat ccggatttgg agatcggtct tgacaagctt 951 tccgtaattc gaaatggtgg tgtacggata atcgataatc gaaaactgtg 1001 ctacacgaaa acgattgatt ggaaacattt gatcacttct tccatcaacg 1051 atgttgtcgt tgataatgct gccgagtacg ctgtcactga gactggattg 1101 atgtgcccac gtggagcttg cgaagaggat aaaggcgaat caaagtgtca 1151 ttatttggag gaaaagaatc aggaacaagg tgtcgaaaga gttcagagtt 1201 gttggtcgaa caccacttgc caaaagtctt gtgcttatga tcgtcttctt 1251 ccaacgaaag aaatcggacc gggatgtgat gcgaacggcg atcgatgtca 1301 cgatcaatgc gtgggcggtt gtgagcgtgt gaatgatgcc acagcatgcc 1351 acgcgtgcaa gaatgtctat cacaagggaa agtgtatcga aaagtgtgat 1401 gctcacctgt accttctcct tcaacgtcgt tgtgtgaccc gtgagcagtg 1451 tctgcagctg aatccggtgc tctcgaacaa aacagtgcct atcaaggcga 1501 cggcaggcct ttgctcggat aaatgtcccg atggttatca aatcaacccg 1551 gatgatcatc gagaatgccg aaaatgcgtt ggcaagtgtg agattgtgtg 1601 cgagatcaat cacgicattg atacgittcc gaaggcacag gcgatcaggc 1651 tatgcaatat tattgacgga aatctgacga tcgagattcg cggaaaacag 1701 gattcgggaa tggcgtccga gttgaaggat atatttgcga acattcacac 1751 gatcaccggc tacctgttgg tacgtcaatc gtcaccgttt atctcgttga 1801 acatgttccg gaatttacga cgtattgagg caaagtcact gttcagaaat 1851 ctatatgcta tcacagtttt tgaaaatccg aatttaaaaa agctattcga 1901 ttcaacgacg gatttgacgc ttgatcgtgg aactgtgtca attgccaata 1951 acaagatgtt atgcttcaag tatatcaagc agctaatgtc aaagttaaat 2001 ataccactcg atccgataga tcaatcagaa gggacaaatg gtgagaaggn 2051 aatctgtgag gatatggcaa tcaacgtgag catcacagcg gtcaacgcgg 2101 actoggtott ctttagttgg coctoattca acattaccga tatagatcag 2151 cgaaagtttc tcggctacga gctcttcttc aaagaagtcc cacgaatcga 2201 tgagaacatg acgatcgaag aggatcgaag tgcgtgtgtc gattcgtggc 2251 agagtgtctt caaacagtac tacgagacgt cgaacggtga accgacccg 2301 gacattttta tggatattgg accgcgcgag cgaattcggc cgaatacgct 2351 ctacgcgtac tatgtggcga cgcagatggt gttgcatgcc ggtgcgaaga 2401 acggtgtatc gaagattggt tttgtgagga cgagctacta tacgcctgat 2451 cctccgacgt tggcactagc gcaagtcgat tcggacgcta ttcatattac 2501 gtgggaagcg ccgctccaac cgaacggaga cctcacgcat tacacaatta 2551 tgtggcgtga gaatgaagtg agcccgtacg aggaagccga aaagttttgt 2601 acagatgcaa gcacccccgc aaatcgacaa cgcacgaaag atccgaaaga 2651 gacgattgta gccgataagc cagtcgatat tccgtcatca cgtaccgtag ctccgacact tttgactatg atgggtcacg aagatcagca gaaaacgtgc



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2751 gctgcaacgc ccggttgttg ttcgtgttcg gctatcgaag aatcatcgga 2801 acagaacaag aagaagcgac cggatccgat gtcggcgatc gaatcatctg 2851 catttgagaa taagctgttg gatgaggttt taatgccgag agacacgatg 2901 cgagtgagac gatcaattga agacgcgaat cgagtcagtg aagagttgga 2951 aaaagctgaa aatttgggaa aagctccaaa aactctcggt ggaaagaagc cgctgatcca tatttcgaag aagaagccgt cgagcagcag caccacatcc 3001 3051 acaccggctc caacgatcgc atcaatgtat gccttaacaa ggaaaccgac 3101 tacggtgccg ggaacaagga ttcggctcta cgagatctac gaacctttac 3151 ccggaagctg ggcgattaat gtatcagctc tggcattgga taatagttat 3201 gtgatacgaa atttgaagca ttacacactt tatgcgattt ctctatccgc 3251 gtgccaaaac atgacagtac ccggagcatc ttgctcaata tcccatcgtg 3301 cgggagcatt gaaacgaaca aaacacatca cagacattga taaagtgttg 3351 aatgaaacaa ttgaatggag atttatgaat aatagtcaac aagtcaacgt 3401 gacgtgggat ccaccgactg aagtgaatgg tggaatattc ggttatgttg taaagcttaa gtcaaaagtc gatggatcaa tigttatgac gagatgigtc 3451 3501 ggtgcgaaga gaggatattc aacacggaat cagggtgtcc tattccagaa tttggccgat ggacgttatt ttgtctcagt aacggcgacc tctgtacacg 3551 gcgctggacc ggaagccgaa tcctccgacc caatcgtcgt catgacgcca 3601 ggettettea etgtggaaat cattetegge atgetteteg tettttigat 3651 tttaatgtca attgccggtt gtataatcta ctactacatt caagtacgct 3701 acggcaaaaa agtgaaagct ctatctgact ttatgcaatt gaatcccgaa 3751 3801 tattgtgtgg acaataagta caatgcagac gattgggagc tacggcagga tgatgttgtg ctcggacaac agtgtggaga gggatcattc ggaaaagtgt acctaggaac tggaaataat gttgtttctc tgatgggtga tcgtttcgga 3851 3901 3951 ccgtgtgcta ttaagattaa tgtagatgat ccagcgtcga ctgagaatct caactatctc atggaagcta atattatgaa gaactttaag actaacttta tcgtccaact gtacggagtt atctctactg tacaaccagc gatggttgtg atggaaatga tggatcttgg aaatctccgt gactatctcc gatcgaaacg 4001 4051 4101 4151 cgaagacgaa gtgttcaatg agacggactg caactttttc gacataatcc 4201 cgagggataa attccatgag tgggccgcac agatttgtga tggtatggcg 4251 tacctggagt cgctcaagtt ttgccatcga gatctcgccg cacgtaattg 4301 catgataaat cgggatgaga ctgtcaagat tggagatttc ggaatggctc gtgatctatt ctatcatgac tattataagc catcgggcaa gcgtatgatg 4351 4401 cctgttcgat ggatgtcacc cgagtcgttg aaagacggaa agtttgactc 4451 gaaatctgat gtttggagct tcggagttgt tctctatgaa atggttacac 4501 tcggtgctca gccatatatt ggtttgagta atgatgaggt gttgaattat 4551 attggaatgg cccggaaggt tatcaagaag cccgaatgtt gtgaaaacta 4601 ttggtataag gtgatgaaaa tgtgctggag atactcacct cgggatcgtc 4651 cgacgttcct ccagctcgtt catcttctag cagctgaagc ttcaccagaa 4701 ttccgagatt tatcatttgt cctaaccgat aatcaaatga tccttgacga 4751 ttcagaagca ctggatcttg atgatattga tgatactgat atgaatgatc 4801 aggttgtcga ggtggcaccg gatgttgaga acgtcgaggt tcagagtgat 4851 tcggaacgtc ggaatacgga ttcaataccg ttgaaacagt ttaagacgat 4901 ccctccgatc aatgcgacga cgagtcattc gacaatatcg attgatgaga 4951 caccgatgaa agcgaagcag cgagaaggat cgctggatga ggagtacgca 5001 ttgatgaatc atagtggagg tccgagtgat gcggaagttc ggacgtatgc 5051 tggtgatgga gattatgtgg agagagatgt tcgagagaat gatgtgccaa 5101 cgcgacgaaa tactggtgca tcaacatcaa gttacacagg tggtggtcca 5151 tattgcctaa caaatcgtgg tggttcaaat gaacgaggag ccggtttcgg tgaagcagta cgattaactg atggtgttgg aagtggacat ttaaatgatg atgattatgt tgaaaaagag atatcatcca tggatacgcg ccggagcacg 5201 5251 5301 ggcgcctcga gctcttccta cggtgttcca cagacgaatt ggagtggaaa 5351 tcgtggtgcc acgtattata cgagtaaagc tcaacaggca gcaactgcag 5401 cagcagcagc agcagcagct ctccaacagc aacaaaatgg tggtcgaggc 5451 gatcgattaa ctcaactacc cggaactgga catttacaat cgacacgtgg 5501 tggacaagat ggagattata ttgaaactga accgaaaaat tatagaaata



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5701 5751	acttgtctga cccacattat	aacccccaaa catatctcta tctgaataat	aaatcccgcc	tcttaaatta	caacggacgt agcatcatcc taaattatct tcagatttt tctgtattt
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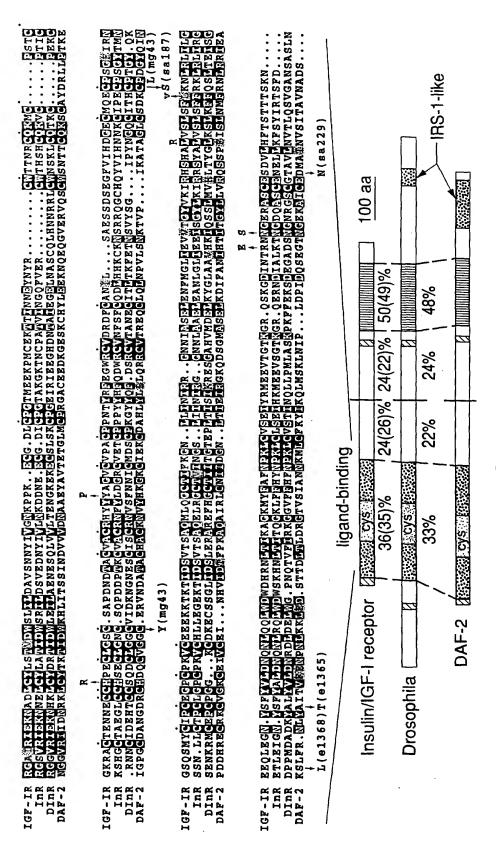
Fig. 2B-3



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Replacement Sheet
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TWIRED TREET TREET TO THE TREET THE TREET THE TREET THE TREET TREE GWWFFFCVAKGVVKDEPET...RV GWWFFCUARDIIKGEAET...RV GWWFECILKSFPPNGVDR...EC GRWFLGTGNNVVSLMGDRFGPC S(e1370 IRS-1-like 100 aa tyrosine kinase 50(49)% L(e1391) 48% 24(22)% 24% ALPVAVILIVGGLVIMLIVPHRREN.NSRIGNGVLYASV<u>NIST</u>FSAAD.....V IGPHITATIVSVVIGSILLFLRRENOPD...GPLYASS<u>NIST</u>LSASDVFPCSV GIGHADIV..SLFGYVCYLHRRKVPSNDH...HMNTEVNITRASMO...... GMLHVDHILMSIAGCIINYYIQVRY.GRRVKALSDFMQLNDDHVCVDNK..... 24(26)% 22% 36(35)% : cys cys cys 33% Insulin/IGF-I receptor Drosophila sa219 DIDR DAF-2 IGF-IR INR DINR IGF-IR INR DinR IGF-IR INR DIDR

Fig. 2C-2



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_	_				
_1	atgaagctaa	tagcaacttc	tcttctagtt	cccgacgagc	acacaccgat
51	gatgtcacca	gtgaatacaa	ctacaaagat	tctacaacoo	agtggtatta
101	aaatggaaat	cccgccatat	ttggatccag	acagtcagga	tgatgacccg
151	gaagatggtg	tcaactaccc	ggatccagat	ttatttgaca	caaaaaacac
201	aaatatgacc	gagtacgatt	tggatgtgtt	gaagcttgga	aaaccagcag
251	tagatgaagc	acggaaaaag	atcgaagttc	ccgacgctag	tacaccacca
301	aacaaaattg	tagaatattt	gatgtattat	agaacottaa	aagaaagtga
351	actcatacaa	ctgaatgcgt	atcggacaaa	acgaaatcga	ttatcottoa
401	acttggtcaa	aaacaatatt	gatcgagagt	tcgaccaaaa	agettgegag
451	tccctggtga	aaaaattgaa	ggataagaag	aatgatctcc	agaacctgat
501	tgatgtggtt	ctttcaaaag	gtacaaaata	taccggttgc	attacaattc
551	caaggacact	tgatggccgg	ttacaggtcc	acggaagaaa	aggtttccct
601	cacgtagtct	atggcaaact	gtggaggttt	aatgaaatga	Caaaaaacca
651	aacgcgtcat	gtggaccact	gcaagcacgc	atttgaaatg	aaaagtgaga
701	tggtatgcgt	gaatccctat	cactacgaaa	ttgtcattgg	aactatgatt
751	gttgggcaga	gggatcatga	caatcgagat	atgccgccgc	Cacatcaaca
801	ctaccacact	ccaggtcggc	aggatccagt	tgacgatatg	agtagattta
851	taccaccagc	ttccattcgt	ccgcctccga	tgaacatgca	cacaaggeet
901	cagcctatgc	ctcaacaatt	gccttcagtt	ggcgcaacgt	ttgcccatcc
951	teteceacat	caggcgccac	ataacccagg	ggtttcacat	ccgtactcca
1001	ttgctccaca	gacccattac	ccgttgaaca	tgaacccaat	tececaaate
1051	ccgcaaatgc	cacaaatgcc	accacctctc	catcagggat	atogaatgaa
1101	tgggccgagt	tgctcttcag	aaaacaacaa	tccattccac	caaaatcacc
1151	attataatga	tattagccat	ccaaatcact	attcctacga	ctataatcca
1201	aacttgtacg	ggtttccaac	tccttatccg	gattttcacc	atcctttcaa
1251	tcagcaacca	caccagccgc	cacaactatc	acaaaaccat	acotcccaac
1301	aaggcagtca	tcaaccaggg	caccaaggtc	aggtaccgaa	tgatccacca
1351	atttcaagac	cagtgttaca	accatcaaca	gtcaccttgg	acotottcco
1401	teggtactgt	agacagacat	ttggaaatcg	attttttgaa	ggagaaagtg
1451	aacaatccgg	cgcaataatt	cggtctagta	acaaattcat	tgaagaattt
1501	gattcgccga	tttgtggtgt	gacagttgtt	cgaccgcgga	tgacagacgg
1551	tgaggttttg	gagaacatca	tgccggaaga	tgcaccatat	catgacattt
1601	gcaagttcat	tttgaggctc	acatcagaaa	gtgtaacttt	ctcaggagag
1651	gggccagaag	ttagtgattt	gaacgaaaaa	tggggaacaa	ttgtgtacta
1701	tgagaaaaat	ttgcaaattg	gcgagaaaaa	atgttcgaga	ggaaatttcc
1751	acgtggatgg	cggattcatt	tgctctgaga	atcgttacag	tctcggactt
1801	gagecaaate	caattagaga	accagtggcg	tttaaagttc	gtaaagcaat
1851	agtggatgga	attcgctttt	cctacaaaaa	agacgggagt	gtttggcttc
1901	aaaaccgcat	gaagtacccg	gtatttgtca	cttctgggta	tctcgacgag
1951	caatcaggag	gcctaaagaa	ggataaagtg	cacaaagttt	acquatotoc
2001	gtctatcaaa	acgtttggct	tcaacgtttc	caaacaaatc	atcagagacg
2051	cgcttctttc	caagcaaatg	gcaacaatgt	acttgcaagg	aaaattgact
		-		5 3 5	



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2101 ccgatgaatt atatctacga gaagaagact caggaagagc tgcgaaggga 2151 agcaacacgc accactgatt cattggccaa gtactgttgt gtccgtgtct 2201 cgttctgcaa aggatttgga gaagcatacc cagaacgccc gtcaattcat 2251 gattgtccag tttggattga gttgaaaatc aacattgcct acgatttcat 2301 ggattcaatc tgccagtaca taaccaactg cttcgagccg ctaggaatgg aagattttgc aaaattggga atcaacgtca gtgatgacta aatgataact 2351 2401 tttttcactc accctactag atactgattt agtcttattc caaatcatcc aacgatatca aactttttcc tttgaacttt gcatactatg ttatcacaag 2451 2501 ttccaagcag tttcaataca aacataggat atgttaacaa cttttgataa gaatcaagtt accaactgtt cattgtgagc tttgagctgt atagaaggac 2551 aatgtatccc atacctcaat ctttaatagt catcagtcac tggtcccgca 2601 2651 ccaattttt cgattcgcat atgtcatata ttgcaccgtg gcccttttta ttgtaacttt taatatattt tcttcccaac ttgtgaatat gattgatgaa 2701 2751 ccaccatttt gagtaataaa tgtattttt gtgg

Fig. 11A-2



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1	gtaatcaaat	tgtaaaggaa	aaatattaat	agtcagagta	cacataaatg
51	ggtgatcatc	ataatttaac	gggccttccc	ggtacctcca	tcccgccaca
101	gttcaactat	tctcagcccg	gtaccagcac	cggaggcccg	ctttatggtg
151	gaaaaccttc	tcatggattg	gaagatattc	ctgatgtaga	ggaatatgag
201		tcggggctgg	_	aatctgctca	atgtaggaaa
251		gttcccgacg	agcacacacc	gatgatgtca	ccagtgaata
301		gattctacaa	cggagtggta	ttaaaatgga	aatcccgcca
351		cagacagtca		ccggaagatg	gtgtcaacta
401		gatttatttg	acacaaaaaa	cacaaatato	accgagtacg
451		gttgaagctt	ggaaaaccaq	cagtagatga	agcacggaaa
501		ttcccgacgc	tagtgcgccg	ccaaacaaaa	ttotagaata
551		tatagaacgt	taaaagaaag	tgaactcata	caactgaatg
601		aaaacgaaat		tgaacttggt	caaaaacaat
651		agttcgacca	_	gagtccctgg	tgaaaaaatt
701		aagaatgatc		gattgatgtg	ottettteaa
751		atataccggt	tgcattacaa	ttccaaggac	acttgatggc
801		tccacggaag	aaaaggtttc	cctcacgtag	tctatoocaa
851		tttaatgaaa	tgacaaaaaa	cgaaacgcgt	catotogacc
901	actgcaagca	cgcatttgaa	atgaaaagtg	acatggtatg	cgtgaatccc
951	tatcactacg	aaattgtcat	tggaactatg	attgttgggc	agagggatca
1001	tgacaatcga	gatatgccgc	cgccacatca	acgctaccac	actccaggtc
1051		agttgacgat	atgagtagat	ttataccacc	agcttccatt
1101	cgtccgcctc	cgatgaacat	gcacacaagg	cctcagccta	tgcctcaaca
1151	attgccttca	gttggcgcaa	cgtttgccca	tcctctccca	catcaggcgc
1201		aggggtttca	catccgtact	ccattgctcc	acagacccat
1251		acatgaaccc	aattccgcaa	atgccgcaaa	tgccacaaat
1301		ctccatcagg	gatatggaat	gaatgggccg	agttgctctt
1351		caatccattc	caccaaaatc	accattataa	tgatattagc
1401		actattccta		ccgaacttgt	acgggtttcc
1451		ccggattttc	accatccttt	caatcagcaa	ccacaccagc
1501		atcacaaaac	catacgtccc	aacaaggcag	tcatcaacca
1551		gtcaggtacc		ccaatttcaa	gaccagtgtt
1601	acaaccatca	acagtcacct	tggacgtgtt	ccgtcggtac	tgtagacaga
1651	catttggaaa	tcgatttttt	gaaggagaaa	gtgaacaatc	cggcgcaata
1701	atteggteta	gtaacaaatt	cattgaagaa	tttgattcgc	cgatttgtgg
1751	tgtgacagtt	gttcgaccgc	ggatgacaga	cggtgaggtt	ttggagaaca
1801	tcatgccgga	agatgcacca	tatcatgaca	tttgcaagtt	cattttgagg
1851	ctcacatcag	aaagtgtaac	tttctcagga	gaggggccag	aagttagtga
1901	tttgaacgaa	aaatggggaa	caattgtgta	ctatgagaaa	aatttgcaaa
1951	ttggcgagaa	aaaatgttcg	agaggaaatt	tccacgtgga	tggcggattc
2001	atttgctctg	agaatcgtta	cagtctcgga	cttgagccaa	atccaattag
2051	agaaccagtg	gcgtttaaag	ttcgtaaagc	aatagtggat	ggaattcgct
			•	- <b></b>	

Fig. 11B-1



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2101 tttcctacaa aaaagacggg agtgtttggc ttcaaaaccg catgaagtac 2151 ccggtatttg tcacttctgg gtatctcgac gagcaatcag gaggcctaaa 2201 gaaggataaa gtgcacaaag tttacggatg tgcgtctatc aaaacgtttg 2251 gcttcaacgt ttccaaacaa atcatcagag acgcgcttct ttccaagcaa 2301 atggcaacaa tgtacttgca aggaaaattg actccgatga attatatcta 2351 cgagaagaag actcaggaag agctgcgaag ggaagcaaca cgcaccactg 2401 attcattggc caagtactgt tgtgtccgtg tctcgttctg caaaggattt 2451 ggagaagcat acccagaacg cccgtcaatt catgattgtc cagtttggat 2501 tgagttgaaa atcaacattg cctacgattt catggattca atctgccagt 2551 acataaccaa ctgcttcgag ccgctaggaa tggaagattt tgcaaaattg 2601 ggaatcaacg tcagtgatga ctaaatgata actttttca ctcaccctac 2651 tagatactga tttagtctta ttccaaatca tccaacgata tcaaactttt tcctttgaac tttgcatact atgttatcac aagttccaag cagtttcaat 2701 2751 acaaacatag gatatgttaa caacttttga taagaatcaa gttaccaact 2801 gttcattgtg agctttgagc tgtatagaag gacaatgtat cccatacctc 2851 aatctttaat agtcatcagt cactggtccc gcaccaattt tttcgattcg 2901 catatgtcat atattgcacc gtggcccttt ttattgtaac ttttaatata 2951 ttttcttccc aacttgtgaa tatgattgat gaaccaccat tttgagtaat 3001 aaatgtattt tttgtgg

Fig. 11B-2

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Replacement Sheet

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1 gtaatcaaat tgtaaaggaa aaatattaat agtcagagta cacataaatg 51 ggtgatcatc ataatttaac gggccttccc ggtacctcca tcccgccaca 101 gttcaactat tctcagcccg gtaccagcac cggaggcccg ctttatggtg 151 gaaaaccttc tcatggattg gaagatattc ctgatgtaga ggaatatgag 201 aggaacctgc tcggggctgg agcaggtttt aatctgctca atgtaggaaa 251 tatggctaat gaatttaaac caataatcac attggacacg aaaccacctc 301 gtgatgccaa caagtcattg gcattcaatg gcgggttgaa gctaatcact 351 ccgaaaactg aagttcccga cgagcacaca ccgatgatgt caccagtgaa 401 tacaactaca aagattctac aacggagtgg tattaaaatg gaaatcccgc 451 catatttgga tccagacagt caggatgatg acccggaaga tggtgtcaac 501 tacceggate cagatttatt tgacacaaaa aacacaaata tgaccgagta 551 cgatttggat gtgttgaagc ttggaaaacc agcagtagat gaagcacgga 601 aaaagatcga agttcccgac gctagtgcgc cgccaaacaa aattgtagaa 651 tatttgatgt attatagaac gttaaaagaa agtgaactca tacaactgaa 701 tgcgtatcgg acaaaacgaa atcgattatc gttgaacttg gtcaaaaaca 751 atattgateg agagttegae caaaaagett gegagteeet ggtgaaaaaa 801 ttgaaggata agaagaatga tctccagaac ctgattgatg tggttctttc 851 aaaaggtaca aaatataccg gttgcattac aattccaagg acacttgatg 901 gccggttaca ggtccacgga agaaaaggtt tccctcacgt agtctatggc 951 aaactgtgga ggtttaatga aatgacaaaa aacgaaacgc gtcatgtgga 1001 ccactgcaag cacgcatttg aaatgaaaag tgacatggta tgcgtgaatc 1051 cctatcacta cgaaattgtc attggaacta tgattgttgg gcagagggat 1101 catgacaatc gagatatgcc gccgccacat caacgctacc acactccagg 1151 tcggcaggat ccagttgacg atatgagtag atttatacca ccagcttcca 1201 ttcgtccgcc tccgatgaac atgcacacaa ggcctcagcc tatgcctcaa 1251 caattgcctt cagttggcgc aacgtttgcc catcctctcc cacatcaggc 1301 gccacataac ccaggggttt cacatccgta ctccattgct ccacagaccc 1351 attacccgtt gaacatgaac ccaattccgc aaatgccgca aatgccacaa 1401 atgccaccac ctctccatca gggatatgga atgaatgggc cgagttgctc 1451 ttcagaaaac aacaatccat tccaccaaaa tcaccattat aatgatatta 1501 gccatccaaa tcactattcc tacgactgtg gtccgaactt gtacgggttt 1551 ccaactcctt atccggattt tcaccatcct ttcaatcagc aaccacacca 1601 gccgccacaa ctatcacaaa accatacgtc ccaacaaggc agtcatcaac 1651 cagggcacca aggtcaggta ccgaatgatc caccaatttc aagaccagtg 1701 ttacaaccat caacagtcac cttggacgtg ttccgtcggt actgtagaca 1751 gacatttgga aatcgatttt ttgaaggaga aagtgaacaa tccggcgcaa 1801 taattcggtc tagtaacaaa ttcattgaag aatttgattc gccgatttgt 1851 ggtgtgacag ttgttcgacc gcggatgaca gacggtgagg ttttggagaa 1901 catcatgccg gaagatgcac catatcatga catttgcaag ttcattttga 1951 ggctcacatc agaaagtgta actttctcag gagaggggcc agaagttagt gatttgaacg aaaaatgggg aacaattgtg tactatgaga aaaatttgca 2001 2051 aattggcgag aaaaaatgtt cgagaggaaa tttccacgtg gatggcggat



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	•				
2101				gacttgagcc	
2151	agagaaccag	tggcgtttaa	agttcgtaaa	gcaatagtgg	atggaattcg
2201	cttttcctac	aaaaaagacg	ggagtgtttg	gcttcaaaac	cgcatgaagt
2251				acgagcaatc	
2301				tgtgcgtcta	
2351				agacgcgctt	
2401				tgactccgat	
2451				agggaagcaa	
2501				tgtctcgttc	
2551	ttggagaagc	atacccagaa	cgcccgtcaa	ttcatgattg	tccagtttgg
2601	attgagttga	aaatcaacat	tgcctacgat	ttcatggatt	caatctgcca
2651	gtacataacc	aactgcttcg	agccgctagg	aatggaagat	tttgcaaaat
2701				taacttttt	
2751				catccaacga	
2801				acaagttcca	
2851				gataagaatc	
2901				aggacaatgt	
2951				ccgcaccaat	
3001				ttttattgta	
3051			aatatgattg	atgaaccacc	attttgagta
3101	ataaatgtat	tttttgtgg			

Fig. 11C-2



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1 cggaagccat ggagctcgag atctgattgc tggacacgga cggaactccg acgtatctcg 61 cagatgcatg ttaacatttt acatccacaa ctgcaaacga tggtcgagca gtggcaaatg 121 cgagaacgcc catcgctgga gaccgagaat ggcaaaggat cgctgctcct ggaaaatgaa 181 ggtgtcgcag atatcatcac tatgtgtcca ttcggagaag ttattagtgt agtatttccg 241 tggtttcttg caaatgtgcg aacatcgcta gaaatcaagc tatcagattt caaacatcaa 301 cttttcgaat tgattgctcc gatgaagtgg ggaacatatt ccgtaaagcc acaggattat 361 gtgttcagac agttgaataa tttcggcgaa attgaagtta tatttaacga cgatcaaccc 421 ctgtcgaaat tagagctcca cggcactttc ccaatgcttt ttctctacca acctgatgga 481 ataaacaggg ataaagaatt aatgagtgat ataagtcatt gtctaggata ctcactggat 541 aaactggaag agagcctcga tgaggaactc cgtcaatttc gtgcttctct ctgggctcgt 601 acgaagaaaa cgtgcttgac acgtggactt gagggtacca gtcactacgc gttccccgaa 661 gaacagtact tgtgtgttgg tgaatcgtgc ccgaaagatt tggaatcaaa agtcaaggct 721 gccaagctga gttatcagat gttttggaga aaacgtaaag cggaaatcaa tggagtttgc 781 gagaaaatga tgaagattca aattgaattc aatccgaacg aaactccgaa atctctgctt 841 cacacgtttc tctacgaaat gcgaaaattg gatgtatacg ataccgatga tcctgcagat 901 gaaggatggt ttcttcaatt ggctggacgt accacgtttg ttacaaatcc agatgtcaaa 961 cttacgtctt atgatggtgt ccgttcggaa ctggaaagct atcgatgccc tggattcgtt 1021 gttcgccgac aatcactagt cctcaaagac tattgtcgcc caaaaccact ctacgaacca 1081 cattatgtga gagcacacga acgaaaactt gctctagacg tgctcagcgt gtctatagat 1141 agcacaccaa aacagagcaa gaacagtgac atggttatga ctgattttcg tccgacagct 1201 tcactcaaac aagtttcact ttgggacctt gacgcgaatc ttatgatacg gcctgtgaat 1261 atttctggat tcgatttccc ggccgacgtg gatatgtacg ttcgaatcga attcagtgta 1321 tatgtgggga cactgacgct ggcatcaaaa tctacaacaa aagtgaatgc tcaatttgca 1381 aaatggaata aggaaatgta cacttttgat ctatacatga aggatatgcc accatctgca 1441 gtactcagca ttcgtgtttt gtacggaaaa gtgaaattaa aaagtgaaga attcgaagtt 1501 ggttgggtaa atatgtccct aaccgattgg agagatgaac tacgacaagg acaattttta 1561 ttccatctgt gggctcctga accgactgcc aatcgtagta ggatcggaga aaatggagca 1621 aggataggca ccaacgcagc ggttacaatt gaaatctcaa gttatggtgg tagagttcga 1681 atgccgagtc aaggacaata cacatatctc gtcaagcacc gaagtacttg gacggaaact 1741 ttgaatatta tgggtgatga ctatgagtcg tgtatcagag atccaggata taagaagctt 1801 cagatgettg teaagaagea tgaatetgga attgtattag aggaagatga acaacgteat 1861 gtctggatgt ggaggagata cattcaaaag caggagcctg atttgctcat tgtgctctcc 1921 gaactegeat tigtgiggae igategigag aactitieeg agetetaigt gaigetigaa 1981 aaatggaaac cgccgagtgt ggcagccgcg ttgactttgc ttggaaaacg ttgcacggat 2041 cgtgtgattc gaaagtttgc agtggagaag ttgaatgagc agctgagccc ggtcacattc 2101 catcttttca tattgcctct catacaggcg ttgaagtacg aaccgcgtgc tcaatcggaa 2161 gttggaatga tgctcttgac tagagctctc tgcgattatc gaattggaca tcgacttttc 2221 tggctgctcc gtgcagagat tgctcgtttg agagattgtg atctgaaaag tgaagaatat 2281 cgccgtatct cacttctgat ggaagcttac ctccgtggaa atgaagagca catcaagatc 2341 atcacccgac aagttgacat ggttgatgag ctcacacgaa tcagcactct tgtcaaagga 2401 atgccaaaag atgttgctac gatgaaactg cgtgacgagc ttcgatcgat tagtcataaa 2461 atggaaaata tggattctcc actggatcct gtgtacaaac tgggtgaaat gataatcgac 2521 aaagccatcg tcctaggaag tgcaaaacgt ccgttaatgc ttcactggaa gaacaaaaat 2581 ccaaagagtg acctgcacct tccgttctgt gcaatgatct tcaagaatgg agacgatctt 2641 cgccaggaca tgcttgttct tcaagttctc gaagttatgg ataacatctg gaaggctgca

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2701 aacattgatt gctgtttgaa cccgtacgca gttcttcaa tgggagaaat gattggaatt 2761 attgaagttg tgcctaattg taaaacaata ttcgagattc aagttggaac aggattcatg 2821 aatacagcag ttcggagtat tgatccttcg tttatgaata agtggattcg gaaacaatgc 2881 ggaattgaag atgaaaagaa gaaaagcaaa aaggactcta cgaaaaatcc catcgaaaag 2941 aagattgata atactcaagc catgaagaaa tattttgaaa gtgtcgatcg attcctatac 3001 tcgtgtgtg gatattcagt tgccacgtac ataatgggaa tcaaggatcg tcacagtgat 3061 aatctgatgc tcactgaaga tggaaaatat gtccacattg atttcggtca cattttggga 3121 cacggaaaga ccaaacttgg gatccagcga gatcgtcaac cgtttattct aaccgaacac 3181 tttatgacag tgattcgatc gggtaaatct gtggatggaa attcgcatga gctacaaaaa 3241 tcaaaacgt tatgcgtcga agcctacgaa gtaatgtgga ataatcgaga tttgttcgtt 3301 tccttgtca ccttgatgct cggaatggag ttgcctgagc tgtcgacgaa agcggatttg 3361 gatcattga agaaaaccct cttctgcaat ggagaaagca aagaagaagc gagaaagttt 3421 ttcgctggaa tctacgaaga agccttcaat ggatcatggt ctaccaaaac gaattggctc 3481 ttccacgcag tcaaacacta ctga

Fig. 15-2



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<b>25590</b> 0000000000000000000000000000000000	339 1110 1110	79 1121 1165 165 165	117 117 117 117 117 117 117 117 117 117	1121 1121 1103 1166
MARKE - NOORN - - CONN -	NSGLG TPPOG HTPDG DLGEK DAAAG	рнио 0	AASMM VGQML EPILL AGCLH	PYSYI NASYA NESYA NISYA SYA
NDDWEETPED NDDWEETPED DPOFESTPED DPOFESTPED -BBBBBBBBBBBBB-	EYSSVPVSNM VYSPV···· ESSNGSTAML ESSNGSTAML OPSEPPEVEP EPSGSAAANP	ТОННЕМИНЬТ	SGMGAMGAQQ SGYGAPGP ATNSSQQQQT EGRS GLCGDFQGPE	SYPHEKP GYRAPAHAKP .TTTRRNAWG LAQKKPNPWG .GGSRRNAWG .SSSRRNAWG
FMNTPDDVMM FMNTPDDVMM PQKAAAIIDE MAEAPQVVEI	WNSYYADTQE W.SYYPEAGE SNEQCGQLGG SNEQCGQLGG AN	NPALGAGLSP SPLPSGPLAP HHHLNQHNNP	VTAMGTALSPGLSGGSSS SPCASGSSTA AAAAAAATG	GGGDAKTFKR GLVHGKEMPK K KRCRKKPTDQ RK
SSVSRFGADT SSVSRFGADT MRIQ	VKMEGHETSD VKMEAHDLAE IPEEDADLYG IPEEDADLYG	TPASFNMSYA YPGGLPA IYQESSATIP	GAMNSMTAAG PGL ASSIGGAQC QAPGSVAAAV	PSNLGRSRAG ESPDDTVSGK QGGGPMPAKK AVTGP
DASSSASTST	INSSPITHEO LNSSPITHEO	MNTMTTSGNM LNPLSSP D ECYTWPMQQY ADFMS	AVAGMPGGSA APAAPLGPTF TTLTSSGSSV SLLEESEDFP	NPCMSPMAYAFRMS MTLGMSINLS PQPGILG PVSQHPPVPP
MMEMLVDQGT MMEMLVDQGT	PMRRPQLEPP PMRRPQLEPP PLPRPEI PLPRPEI	SMNSMNTYMT TMAPLNSYMT SNSHQTSFPS SNSHQTSFPS VHT	LPQPLLNLNM	NGLGPYAAAM AASVPCSSG PSRLSEPAGG PAPPQPPPG
Hnf3a Hnf3g D16123a467891011 D1612567891011 Afx Fkhr Consensus	Hnf3a Hnf3g D16123a467891011 D1612567891011 Afx Fkhr Consensus	Hnf3a Hnf3g D16123a467891011 D1612567891011 Afx Pkhr Consensus	Hnf3a Hnf3g D16123a467891011 D1612567891011 Afx Fkhr Consensus	Hnf3a Hnf3g D16123a467891011 D1612567891011 Afx Fkhr Consensus



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222 221 330 330 330	22 2 2 2 2 3 3 3 3 3 3 3 3 3 3 3 3 3 3	3321 3321 3312 3312 440	3376 331 331 371 495	46646464646464664664664646464646464646
LOCKHS LOCKHS LOCKHS LOCKHS LOCKHS LOCKHS LOCKHS	KRFKC KRFKL KSRRG KSRRG KS	KTGQL FRPRT FRPRT FRPRS FRPRT FRPRT	PASHP BGL NPENM	GASSA GASA GAS GAS
WONSIRHS AGWKNSIRHN AGWKNSIRHN AGWKNSIRHN AGWKNSIRHN AGWKNSIRHN	FUNGCYLRRO FUNGCYLRRO IDTTTKAQLE IDTTTKAQLE MUNSSSKILLRG MUNNSKFAKS	DSPLHRGVHG QGAFDNVPSS QGAFDNVPSS NREEADMWTT SNDDFDNWST	SSGPGALASV PAIGS PAIGS GGVPPTLN STLPSLSEIS	LDFKAYEQAL LDVV FSLQHPGVTG TSLNSPSPNY
RONDOR RONDOR BROKEDSNSS BROKEDSNSS EXDKEDSNSS EXDKEDSNSS EXDKEDSNSS	PRRTRERSINT PRRTRERSINT PRR	DPSGASNPSA AATVTSPP SHDLYDDDSM SHDLYDDDSM AKWSGSPCSR SKWPASPGSH	TPASSTAPPI TPASSTP IPGSS.SRVS IPASV.SSYA YPPSA.AKMA -P-SS	MSS.SEQQHK MSEQTPAPPKTPCYSFAPPN TPCYSFAPPN
YOWINDLEPY YOWINDLEPY YOWFSDNIPY YOWFSDNIPY YEWNVRTVPY YEWNVRTVPY	HPDSG NPDSG NPDSKPGMN NPEGGKSGKA NPEGGKSGKA	GAKGGPESRK TGSAASTTTP NSIAGSIQTI NSIAGSIQTI ATPTSPVGHF AG. DSPGSQF	TATGGASELK LDCGS LAEE LGEGDVHSMV	FNHPFSINNL PAIP PAIP LSG QSSEGTMMQQ
PSKMPPPSET PGKVPPPSET PDGKPPPOK PDGKPPPO PEKKPPPSOT AEKKPPPSOT	KPGKGSWWTF KPGKGSWWAF GAGKSSWWV GAGKSSWWW ATGKSSWWMF GTGKSSWWMF	GGGGSGSGGS GSGASTTRNG MGSMHSTLNG MGSMHSTLNG SVMPAPPEG S HQSGQEG	SPQTLDHSGA EAQGGEDVGA  LSPLRPESEV LSPIMTEQDD	CHLKGDPHYS GDLKLDAPYN . PSWVGESV . PSWVGESV SSHSLLSREG SSPTSLLSREG SSPTSLLSREG
STITMATORA STITMATORA ELINTAIMAS DITAKALESA ENTSOATESA DITTMATESSA INTERNATESSA	CEVKUARSP CEVKUARSP REMREON REIKUHN KEIRUON KEIRUON FE U-	EKQPGAG EEKVKG AKKRIKERAL AKKRIKERAL KKKP	EGAPAPGPAA OPPPPAPEP OSNLS SSNASSVSTR SSNASSTISGR SSNASTISGR	AHGLAPHESQ .YFTGMELP .DIYDDMEF. .DIYDDMEF. E.LLDGMLT ENLLDMENLL
Hnf3a Hnf3g D16123a467891011 D1612567891011 Afx Fkhr Consensus	Hnf3a Hnf3g D16123a467891011 D1612567891011 Afx Fkhr	Hnf3a Hnf3g D16123a467891011 D1612567891011 Afx Fkhr Consensus	Hnf3a Hnf3a D16123a467891011 D1612567891011 Afx Fkhr Consensus	Hnf3a Hnf3g D16123a467891011 D1612567891011 Afx Fkhr Consensus

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0 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2		GOHIHADI GLOFNGEPOP TLOFNGEPOP 	Fig. 21A-3	ፋ <b>ፈጀ</b> ህ ፣	MPQDLDLDMY LPSDLD.GMF 	GRMGLLHQEK	23a4678 6125678 Cons 23a4678 6125678
てきまる	• • • •		LENHELSOAG	• • •			Hnf Hnf 123a4678910
44 44 44 44 44 44 44 44 44 44 44 44 44	S C N G Y	PVLTPPTEAA SALGGYSSVS	DOPLMDTM DQPLMDTM APIPKALGT QVPLPHPMQM	PIDLENLTLP PIDLENLTLP AS	OHTVASSSAL QHTVASSSAL LSMIAPPPVM VSTMPHTSGM	GIQSCGIVAA GIQSCGIVAA ARGPSSLVPT AVNGRPLPHT	Hnf3a Hnf3g D16123a467891011 D1612567891011 Afx Fkhr
4645466 6457466 676666 67666	SSSPICE SSPICE AQUID AQUID I	TPINWLSTSN TPINWLSTSN TGVGLC NPSSHTHPGH	AYGNYQNGGI AYGNYQNGGI LPSS.SKLA QASH.NKMM	• • ១៨១១១ ខ	LHRNPIVPS LLE RVEGONVMMG	VRGSCAONP. VDPILSOAPT VDPGVAOPNS VDPGVAOPNS	Hnf3a Hnf3g 6123a467891011 D1612567891011 Afx Fkhr Consensus
4883849 748849 74886 7486 7486 7486 7486 7486 7486 748	HELNS HELNS HELNS VLMTQ DIMTP	NTS NAS MEPIAPPSY MEDIAPPPSY MSDSPEH.N	YQGVYSRPVE YQGLYSRSLE IKQESKPIK IKQESKPIK SSSQALEALE CAPGLLKELE	IEPSWLEPAYGGEPGVY THIGGVQ THIGGVQ GPLSMGEGCF SSYGGMSQYN	GSASVTTRSP RTDQMRIDAT RTDQMRIDAT MPIQTLQDNR	GSTLPASLPL GAE SSLFSP GQSSMSPLPQ	Hnf3a Hnf3g 6123a467891011 D1612567891011 Afx Fkhr Consensus